Stroke

ORIGINAL CONTRIBUTIONS

Early Thrombectomy Protects the Internal Capsule in Patients With Proximal Middle Cerebral Artery Occlusion

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BACKGROUND AND PURPOSE: Proximal middle cerebral artery (MCA) occlusions impede blood flow to the noncollateralized lenticulostriate artery territory. Previous work has shown that this almost inevitably leads to infarction of the dependent gray matter territories in the striate even if perfusion is restored by mechanical thrombectomy. Purpose of this analysis was to evaluate potential sparing of neighboring fiber tracts, ie, the internal capsule.

METHODS: An observational single-center study of patients with proximal MCA occlusions treated with mechanical thrombectomy and receiving postinterventional high-resolution diffusion-weighted imaging was conducted. Patients were classified according to internal capsule ischemia (IC+ versus IC−) at the postero-superior level of the MCA lenticulostriate artery territory (corticospinal tract correlate). Associations of IC+ versus IC− with baseline variables as well as its clinical impact were evaluated using multivariable logistic or linear regression analyses adjusting for potential confounders.

RESULTS: Of 92 included patients with proximal MCA territory infarctions, 45 (48.9%) had an IC+ pattern. Longer time from symptom-onset to groin-puncture (adjusted odds ratio, 2.12 [95% CI, 1.19–3.76] per hour), female sex and more severe strokes were associated with IC+. Patients with IC+ had lower rates of substantial neurological improvement and functional independence (adjusted odds ratio, 0.26 [95% CI, 0.09–0.81] and adjusted odds ratio, 0.25 [95% CI, 0.07–0.86]) after adjustment for confounders. These associations remained unchanged when confining analyses to patients without ischemia in the corona radiata or the motor cortex and here, IC+ was associated with higher National Institutes of Health Stroke Scale motor item scores (β, +2.8 [95% CI, 1.5 to 4.1]) without a significant increase in nonmotor items (β, +0.8 [95% CI, −0.2 to 1.9).

CONCLUSIONS: Rapid mechanical thrombectomy with successful reperfusion of the lenticulostriate arteries often protects the internal capsule from subsequent ischemia despite early basal ganglia damage. Salvage of this eloquent white matter tract within the MCA lenticulostriate artery territory seems strongly time-dependent, which has clinical and pathophysiological implications.

Key Words: basal ganglia ■ perfusion ■ reperfusion ■ thrombectomy ■ white matter

Mechanical thrombectomy is the standard of care for patients with acute ischemic stroke because of a large vessel occlusion in the anterior circulation.[1–6] Recently, the scientific focus has shifted toward a more detailed analysis on how to further maximize clinical benefit and technical safety and elucidate determinants of good clinical outcomes.

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Nonstandard Abbreviations and Acronyms

CT	computed tomography
DWI	diffusion-weighted imaging
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times
HERMES	Highly Effective Reperfusion Using Multiple Endovascular Devices
INTERRSeCT	Identifying New Approaches to Optimize Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV tPA Using Serial CT Angiography
IQR	interquartile range
MCA	middle cerebral artery
MRI	magnetic resonance imaging
MT	mechanical thrombectomy
NIHSS	National Institutes of Health Stroke Scale
r-tPA	recombinant tissue-type plasminogen activator

Proximal middle cerebral artery (MCA) occlusions and subsequent infarction of the striatocapsular region supplied by the MCA lenticulostriate arteries have been associated with a worse outcome.[7,8] This association has been attributed to the infarction of eloquent white matter tracts passing through the striatocapsular territory (eg, pyramidal tract).[8,9] Because the striatocapsular region is supplied by noncollateralized end arteries,[10] infarction in this area occurs relatively early and hence, is seldom completely avoidable, even in cases of successful reperfusion.[11,12] However, tissues within the striatocapsular region might have different resistances to hypoxia because white matter tracts may survive longer than grey matter.[13–15] Infarct growth and initial mismatch, indicating potentially salvageable tissue were indeed shown to be substantially larger in white matter than in gray matter.[16] Furthermore, evidence derived from r-tPA (recombinant tissue-type plasminogen activator) lysis and mechanical thrombectomy studies suggests that successful recanalization was associated with preferential salvage of the white matter as compared with gray matter in the MCA territory.[17,18] Within this study, we evaluated if rapid mechanical thrombectomy is capable of protecting the internal capsule at the level supplied by the MCA lenticulostriate arteries and if this salvage is associated with a clinical benefit.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request and after clearance by the local ethics committee.

Study Population

All consecutive isolated MCA occlusion subjected to angiography between January 2007 and June 2016 and available follow-up imaging were evaluated (n=325). After the exclusion of patients without lenticulostriate artery occlusions and/or patients with follow-up computed tomography (CT) only, 92 patients receiving post-interventional magnetic resonance imaging (MRI) with high-resolution diffusion-weighted imaging (DWI) constituted the final study population. The local ethics committee approved this retrospective study waiving informed consent.

Endovascular Therapy

Patients were generally eligible for endovascular therapy during the study period if they met the following inclusion criteria:

- National Institutes of Health Stroke Scale (NIHSS) >3
- Symptom-onset to groin puncture <6 hours
- Demarcation on native CT <1/3 of the MCA territory
- CT/MR angiography proven large vessel occlusion in the anterior circulation

Nearly half of the patients were transferred from remote hospitals (drip-and-ship, n=50%, n=46). In cases of transfer from another hospital, usually, no additional CT imaging was performed before the thrombectomy procedure. Patients received intravenous r-tPA bridging in the absence of contraindication (70.7%, n=65). Patients were treated under conscious sedation or general anesthesia using transfemoral access and standard tri-axial approach with a distal aspiration catheter as described before.[19] One patient was treated with a first-generation Penumbra Aspiration System (The Penumbra System, Penumbra, Alameda, CA). In 2 patients, spontaneous reperfusion occurred and in 3 patients, intracranial access could not be established owing to difficult supraaortic vessel configuration/elongation. All other patients were treated with second-generation devices, mostly stent-retrievers (n=76, Solitaire AB, eV3, Irvine, CA Solitaire, Medtronic, Trevo, Stryker, pRESET thrombectomy device, Phenox), large bore aspiration catheters (n=5, eg, 5MAX, Penumbra) or a combination thereof (n=5). In 2 patients, additional intraarterial tPA was infused as rescue therapy.

Image Analysis

Digital Subtraction Angiography

Perfusion of the lenticulostriate arteries was evaluated on the first digital subtraction angiography runs acquired before thrombectomy, according to 3 patterns as previously described (Figure 1).[11] If no, or only the most proximal group of the MCA lenticulostriate arteries was visible on the first angiography runs, this was rated as complete occlusion of the lenticulostriate arteries relevant for superior internal capsule supply (Figure 1A and 1B).[11] In this occlusion pattern, flow to the upper part of the internal capsule cannot be expected.[20,21] If any of the medial or lateral lenticulostriate artery groups were already partially perfused on first angiography runs, this was rated as partial or no lenticulostriate artery occlusion (residual flow to the upper part of the internal capsule can be expected, see Figure 1C or no lenticulostriate artery is occluded).[20,21] This dichotomization was made according to results by Donzelli et al[21] and Rosner et al,[20] suggesting that the entire anteroposterior length of the upper part of the internal capsule is supplied by the medial and lateral

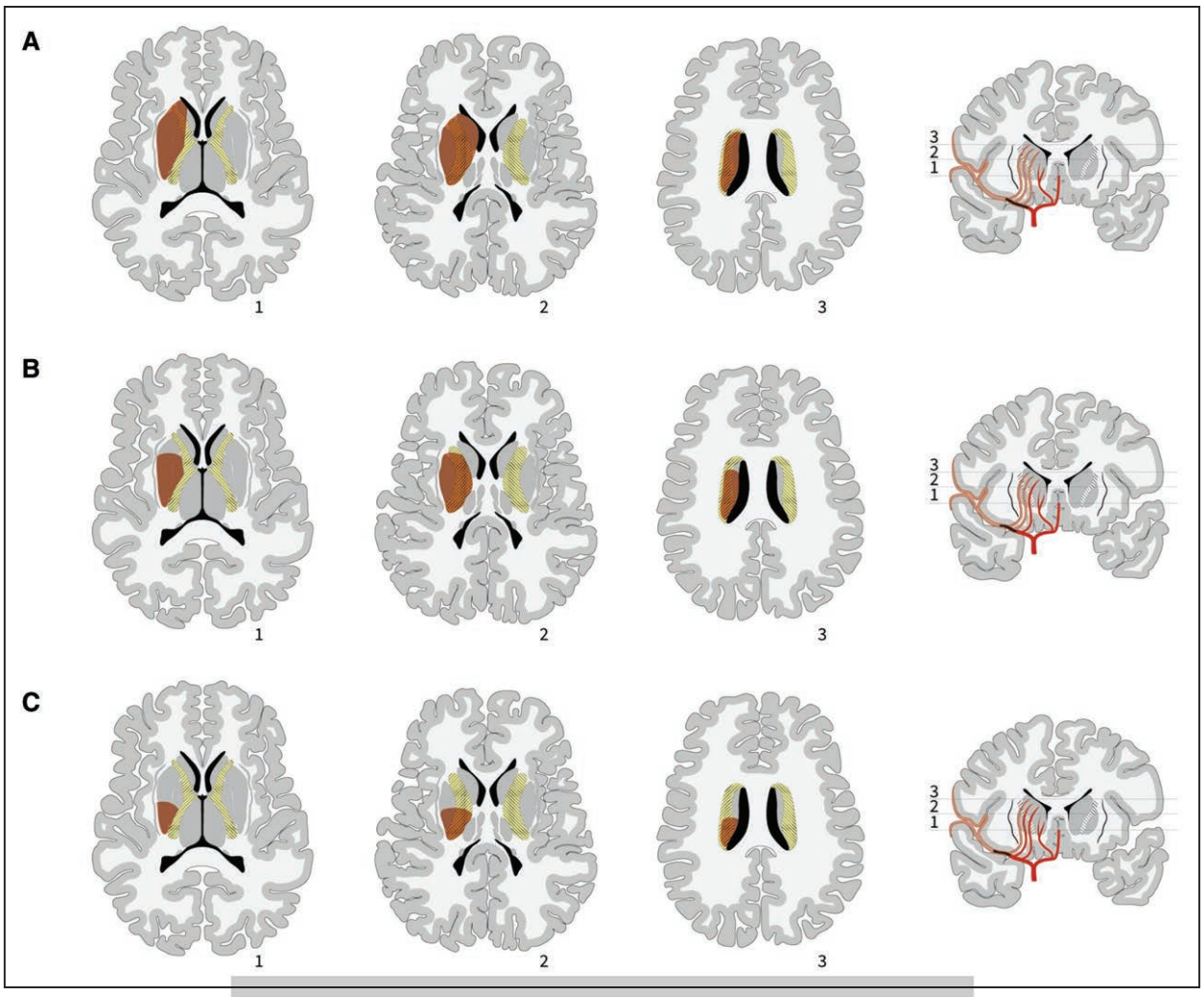

Figure 1. Involvement of the internal capsule depending on the middle cerebral artery (MCA) occlusion location and occlusion of the lenticulostriate orifices.

The inferior part of the posterior limb of the internal capsule is usually supplied by the anterior choroidal artery while almost the entire anteroposterior length of the superior part of the internal capsule is supplied by the lateral and middle groups of lenticulostriate arteries. Involvement of the upper part of the internal capsule is almost complete in occlusion patterns (**A**) and (**B**), while residual flow to the upper part of the internal capsule can be expected in the distal occlusion pattern (**C**; cf. methods for further details and rational). Generally, internal capsule involvement in MCA lenticulostriate artery occlusion is typically superior (slice 2 and 3) and not seen at the level of the thalamus (1).

lenticlostriate artery group. Hence, complete occlusion of the medial and lateral lenticulostriate artery group should result in a severe reduction of blood flow to the upper part of the internal capsule. In contrast, the internal capsule remains partially perfused if the medial and/or lateral lenticlostriate arteries orifices are not occluded.

Final mechanical thrombectomy reperfusion success was graded according to the Thrombolysis in Cerebral Infarction scale with Thrombolysis in Cerebral Infarction score of 2b/3 defined as successful reperfusion. Successful reperfusion of the lenticulostriate arteries was defined as reperfusion of all lenticulostriate arteries including the lateral group.[11,20] The following time points were assessed: groin puncture, the time point of reperfusion of all lenticulostriate arteries, and the time point of final reperfusion achieved.

Admission CT

Admission CT data were available in 46 patients only (see above, drip-and-ship). In 45 patients, collateral grading according to the methods outlined by the MR CLEAN investigators was performed.[22] For this purpose, patients were classified using a 4-step grading system ranging from 0 (0% filling of the occluded territory) to 3 (100% filling of the occluded territory).[22]

Follow-Up MRI

Infarction of the internal capsule was evaluated at the level and shortly before the fiber tracts pass through the gray matter bridges between the caudate and the putamen on coronal-reformatted high-resolution DWI (Figure 2). This area is known as the postero-superior lenticulostriate artery territory, supplied by the most lateral or rarely intermediate MCA lenticulostriate artery group.[9,20,21,23–25] The presence (IC+) or absence (IC–) of internal capsules ischemia at this level was evaluated on postinterventional 3T DWI sequences and corresponding apparent diffusion coefficient maps (Figure 2). DWI was performed by using a double refocused spin-echo echo-planar DWI sequence on the axial plane, with the following

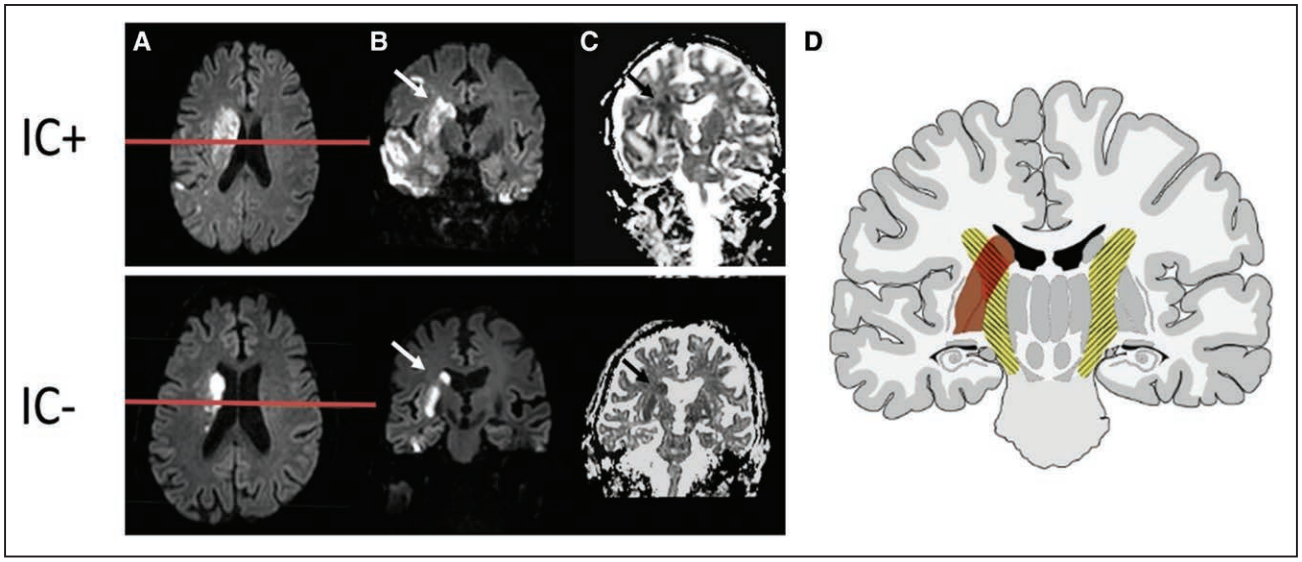

Figure 2. Involvement and sparing of the internal capsule.
A-**C**, Internal capsule sparing (IC−) or ischemia (IC+) at the posterosuperior level. The latter is shown by continuous diffusion restriction from the putamen to the caudate body on axial (**A**) and coronal DWI (**B**) as well as corresponding apparent diffusion coefficient map (**C**). Red lines on axial diffusion-weighted imaging correspond to the level of coronal reformatting. **D**, Schematic representation of an IC+ pattern.

parameters: (b-value=1000 seconds/mm^2; TR=7695 ms; TE=55 ms; flip angle: 90°; matrix: 256×256×73; voxel size, mm: 0.875×0.875×2; slice thickness: 2 mm without a gap). Grading was performed by 2 raters, including 1 neuroradiologist with >3 years of experience. A consensus read was performed in cases of discrepancies. Hemorrhagic transformation within the putamen was evaluated on T2* sequences (Figure I in the Data Supplement). Additionally, infarction in the white matter territory above the basal ganglia (corona radiate/centrum semiovale) and involvement of the motor cortex was assessed (see Figure II in the Data Supplement). Final infarct volume was evaluated using a threshold-based semiautomated algorithm of the Insight Segmentation and Registration Toolkit (ITK-snap).[26] Manual corrections were performed in cases of inadequate segmentations, leading to the volume measurements used for subsequent analyses (see Figure III in the Data Supplement).

Clinical Outcome

NIHSS on admission and day 7 or discharge were evaluated by a qualified vascular neurologist. Motor items (facial, arm, limb) were extracted from medical charts separately. Functional outcome was assessed at discharge and day 90 using the modified Rankin Scale. Functional assessment at discharge and day 90 was available in 86/92 and 70/92, respectively. Functional independence was defined as modified Rankin Scale score ≤2. Substantial neurological improvement was defined as either NIHSS at discharge ≤1 or difference between NIHSS at discharge and on admission ≥8.[27] Patients who died during the acute hospital stay were assigned an NIHSS score of 42.

Statistical Analysis Plan

Continuous and ordinally scaled variables are displayed as median (interquartile range [IQR]), while frequency counts are presented as n/N (%). Independent group comparisons were performed using Mann-Whitney *U* test or Fisher exact test. To identify independent associations of baseline variables with IC+ versus IC−, we used a logistic regression model including all variables with $P<0.200$ on univariable comparison. To display an association of IC+ versus IC− with increasing symptom-onset to groin puncture or symptom-onset to lenticulostriate artery reperfusion intervals, we plotted predicted probabilities of the logistic regression models holding all other included variables at mean (continuous variables) or at balance (categorical variables). Logistic regression models with clinical end points as dependent variables were generally adjusted for age, admission NIHSS (per point increase), final infarct volume (per cc increase), reperfusion success, and intravenous thrombolysis. The significance level was set to $\alpha<0.05$. All tests are 2-sided. All statistical analyses were performed using standard software packages (Stata, version 15.1; StataCorp or SPSS Statistics version 25, IBM).

RESULTS

Ninety-two patients with adequate postinterventional DWI were included (median age, 73 years; IQR, 58–81 years; 58.7%, 54/92 female). Successful recanalization was achieved in 80 patients (87.0%) while reperfusion of the proximal M1 segment with subsequent restoration of complete MCA lenticulostriate artery flow was observed in 89 patients (96.7%). Median time from symptom onset to groin puncture, reperfusion of all lenticulostriate arteries, and final reperfusion success was 215 minutes (IQR, 175–265 minutes), 234 minutes (IQR, 199–299 minutes), and 269 minutes (IQR, 207–320 minutes), respectively. All patients showed striatal ischemia. In 45 patients (48.9%), postinterventional MRI revealed involvement of the internal capsule (IC+). Concerning the dichotomization of IC+ versus IC−, interrater agreement was near-perfect (Cohen κ=0.89). The median time from thrombectomy to postinterventional MRI was 3 days (IQR,

1–4 days). Patients presented with a median baseline NIHSS of 14 (IQR, 12–16) and improved to an NIHSS of 6 (IQR, 2–10) at day 7 or day of discharge. Functional independence at discharge and day 90 was observed in 41.9% (36/86) and 72.9% (51/70), respectively.

Determinants of IC Ischemia

All patients without reperfusion of the MCA perforators had an IC+ pattern (n=3). In more than half of patients with complete reperfusion of the lenticulostriate arteries, IC− was observed (47/89). Despite striatocapsular territory ischemia on postinterventional DWI, 37 patients showed partial perfusion of the MCA perforators as revealed by first DSA runs before thrombectomy, possibly because the thrombus had migrated.[28] Patients with partial perfusion of the MCA perforators before thrombectomy were numerically more likely to have an IC− pattern as opposed to patients without spontaneous reperfusion of the lenticulostriate arteries (56.4% versus 37.8%; P=0.093). Time from symptom onset to groin puncture and delays from symptom onset to reperfusion of the lenticulostriate arteries was lower in the IC− group (median, 210 versus 221 minutes, P=0.033 minutes and median 209 versus 247 minutes, P<0.001). In 45 patients with available collateral grade status, collateral grade did not differ between IC+ and IC− patients (2, IQR, 1–3 versus 2; IQR, 2–2, P=0.664). After correcting for other baseline differences with P<0.200 in univariable comparison, there was an association between symptom-onset to groin puncture and IC+ (adjusted odds ratio [aOR], 2.12 [95% CI, 1.19–3.76] per hour, P=0.010, Table 1). Using the same model in patients with occluded lenticulostriate arteries on admission imaging, every hour delay in symptom-onset to lenticulostriate artery reperfusion increased the Odds for IC+ (3.47 [95% CI, 1.52–7.89]; P=0.003). Predicted probabilities of IC+ versus IC− with increasing time from symptom-onset to lenticulostriate artery reperfusion and symptom onset to groin puncture intervals are shown in Figure 3 and Figure IV in the Data Supplement.

Clinical Impact of Salvaging the IC

IC+ patients had more putaminal hemorrhages (55.6% versus 17%, P<0.001, Table 2), and NIHSS scores on the day of discharge or day 7 were higher (median 7 versus 3, P<0.001). Moreover, patients with IC+ tended to have lower rates of substantial neurological improvement (45.5% versus 67.4%, P=0.055) and achieving functional independence on discharge or day 90 was less likely (26.8% versus 55.6%; P=0.009 and 55.6% versus 91.2%; P<0.001). For these end points, associations remained statistically significant, when adjusting for potential confounders including age, admission NIHSS, intravenous thrombolysis, reperfusion grade, and final infarct volume (aOR, 0.26 [95% CI, 0.09–0.81]; aOR, 0.25 [95% CI, 0.07–0.86]; and aOR, 0.17 [95% CI, 0.03–0.89], respectively).

To increase the specificity for evaluating the effect of IC+, we confined a subanalysis to cases without white matter tract involvement of the internal capsule above the level of the striatocapsular region and/or ischemic lesions within the motorcortex. In this subgroup (n=51, 23 IC+, 28 IC−), IC− patients had lower NIHSS scores on the day of discharge (median 1 versus 7, P<0.001). The lower NIHSS scores were mainly attributable to lower score on the motor items (median motor sum 0 versus 4, median facial: 0 versus 1, P<0.001, arm: 0 versus 2, P<0.001 and leg: 0 versus 1, P<0.001). These differences remained significant on linear regression analyses after adjusting for the same clinical covariates used for the binary logistic regression model about the main clinical outcomes (Table I in the Data Supplement).

DISCUSSION

This study shows 4 major findings. First, endovascular reperfusion may salvage the internal capsule at the level supplied by the MCA lenticulostriate arteries despite ischemia in the putamen and the caudate nucleus, providing further evidence for higher ischemic resistance of white matter within this area. Second, salvage of the capsule is clearly time-dependent, most likely reflecting the noncollateralized end artery supply in this territory. Third, putaminal hemorrhage may be associated with internal capsule infarction potentially because both phenomena are related to prolonged and/or more severe ischemia and hence, more severe tissue damage. Fourth, protection of the internal capsule was associated with a clinical benefit (ie, mainly of motor functions) in patients with and without ischemia above the level of the basal ganglia.

Multiple studies suggested that infarct growth is distinctly different between cerebral gray and white matter[16,29] because ischemic tolerance is higher in white matter.[13,29–31] Correspondingly, white matter tracts may be protected from ischemia by early reperfusion, despite gray matter ischemia in the same territory.[17,18] In this study, we specifically examined, if these associations are also tangible in the noncollateralized proximal MCA territory. For this purpose, we evaluated infarction of the internal capsule at the posterosuperior lenticulostriate artery territory encompassing the corticospinal tract.[9] While there is some heterogeneity regarding the supply of the posterior limb of the internal capsule at different levels, the entire anteroposterior length of the upper part of the internal capsule is supplied by the lateral and intermediate groups of lenticulostriate arteries arising from the middle cerebral artery.[20,23–25] As repeatedly reported by microstructural cadaver studies, there are no or very few anastomoses between the different lenticulostriate artery groups.[20,23,32] Specifically, Rosner et al[20] did not observe

Table 1. Baseline Characteristics With Strata of IC− Versus IC+

Baseline characteristics	IC− (n=47)	IC+ (n=45)	*P* value	Logistic regression model: adjusted OR (95% CI)
Age	73.9 (65.0–81.1)	72.8 (49.4–81.6)	0.316	0.98 (0.95–1.01)
Sex, female	51.1% (24)	66.7% (30)	0.144	3.36 (1.11–10.19)*
IV r-tPA	72.3% (34)	68.9% (31)	0.820	Not included
Baseline NIHSS (n=91)	13 (9–15)	15 (13–17)	0.036*	1.20 (1.04–1.39)*
ASPECTS (n=46)	9 (7–10)	8 (7–9)	0.525	Not included
CTA-collaterals (n=45)	2 (1–3)	2 (2–2)	0.664	Not included
Partial perfusion of LSA on admission	48.9% (23/47)	31.1% (14/45)	0.093	0.68 (0.24–1.92)
Successful reperfusion of LSA after MT	100% (47/47)	93.3% (42/45)	0.113	Did not converge
Symptom-onset to groin puncture, min	210 (168–240)	221 (186–273)	0.033*	2.12 (1.19–3.76) per hour*
Symptom-onset to LSA reperfusion, min	209 (172–253)	247 (227–333)	0.002†	Omitted (co-linearity)
Successful reperfusion (TICI2b/3)	91.5%	82.2%	0.226	Not included
Symptom-onset to final reperfusion, min	248 (190–288)	289 (234–350)	0.007†	Omitted (colinearity)
Time to follow-up MRI, d	3 (2–4)	2 (1–4)	0.148	0.93 (0.73–1.19) per day
Diabetes	12.8% (41/47)	13.3% (6/45)	>0.999	Not included
Hypertension	72.3% (34/47)	75.6% (34/45)	0.814	Not included
Atrial fibrillation	48.9% (23/47)	44.4% (20/45)	0.682	Not included
History of stroke or TIA	14.9% (7/47)	13.6% (6/45)	>0.999	Not included

IC−/IC+ refer to sparing and involvement of the internal capsule, respectively. ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; CTA, computed tomography angiography; IV tPA, intravenous tissue-type plasminogen activator; LSA, lenticulostriate artery; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; r-tPA, recombinant tissue-type plasminogen activator; TIA, transient ischemic attack; and TICI, Thrombolysis in Cerebral Infarction.

*P<0.05, †P<0.01.

a single anastomose between the lateral lenticulostriate arteries and any other group of perforating arteries studied in 50 cadaver hemispheres. Correspondingly, we found a strong time-dependency of the IC+ pattern corroborating findings that the proximal MCA territory is not or at best poorly collateralized. We also found no impact of collateral status; however, this analysis was confined to a subset of patients only. In contrast to deep gray matter structures, which showed signs of ischemia in all included patients and have been reported to almost exclusively undergo infarction despite early reperfusion,[11] nearly half of the patients did not show signs of IC ischemia on post-interventional DWI. Nevertheless, the predicted probabilities of IC+ were >80% after 5 hours, and the maximum time from symptom-onset to lenticulostriate artery reperfusion observed in a patient with an IC− pattern was 325 minutes. Of course, this does not imply that thrombectomy is not beneficial beyond this time window in patients with proximal occlusions[33,34]; however, its benefit may be reduced and may potentially be more time-dependent.[35] It is important to stress that the reported observations are of mere qualitative nature and dichotomization may not adequately reflect gradually changing damage of the corticospinal tract over time. This may also explain why IC+ ischemia patients showed significant heterogeneity concerning their neurological deficits (interquartile range of NIHSS day 7/discharge 4-13). Another explanation for this heterogeneity may be pervious thrombi allowing residual flow through macroscopically occluding thrombi, which has been associated with good outcomes.[36]

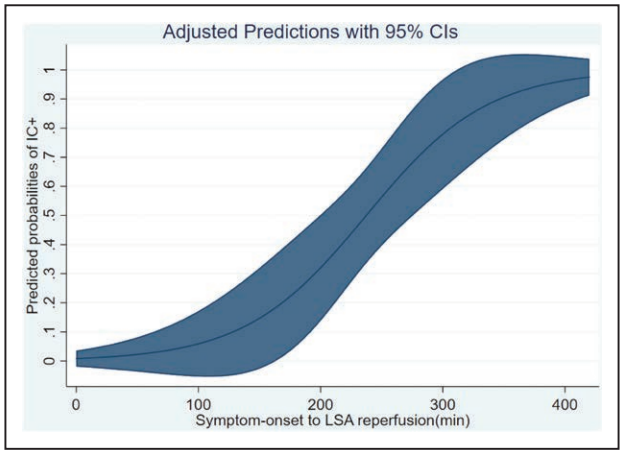

Figure 3. Time dependency of internal capsule ischemia predicted probabilities of IC+ with increasing symptom-onset to lenticulostriate artery reperfusion intervals.
Beyond 5 h (300 min), an IC+ pattern is likely (>80%, depending on the model, cf. methods for further detail). The increase in the odds of an IC+ pattern with time was considerable (adjusted odds ratio per hour delay, 3.47 [95% CI, 1.52–7.89]). LSA indicates lenticulostriate arteries.

We found a strong association of IC+ pattern and clinical outcomes, which was driven by increased motor deficits. Several studies have investigated the correlation of acute corticospinal tract injury and patients' motor and functional outcomes.[37–40] It is well known that infarct volume alone is a mediocre predictor of functional outcomes in patients with large vessel occlusions[41] and a

Table 2. Tissue and Clinical Outcomes of Patients With Strata of IC+ Versus IC− Pattern

Outcome variables	IC− (n=47)	IC+ (n=45)	*P* value
Hemorrhagic transformation (Putamen)	17.0% (8/47)	55.6% (25/45)	<0.001*
Infarct volume, cc	14.9 (4.8–67.9)	21.7 (10.7–78.0)	0.068
Median NIHSS on day 7 or discharge	3 (0–7)	7 (4–13)	<0.001*
Early neurological improvement	67.4% (31/46)	45.5% (20/44)	0.055
Discharge mRS	2 (1–3)	4 (2–5)	<0.001*
Functional independence at discharge	55.6% (25/45)	26.8% (11/41)	<0.009*
Functional independence at discharge 90 d	91.2% (31/34)	55.6% (20/36)	<0.001*

IC−/IC+ refer to sparing and involvement of the internal capsule. Functional independence was defined as mRS score ≤2. mRS indicates modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.
*P<0.01.

post hoc analysis of HERMES (Highly Effective Reperfusion Using Multiple Endovascular Devices) revealed that only 12% of the relationship between the endovascular treatment effect and functional outcomes are mediated by infarct volume.[42] Neurological and functional outcomes depend considerably on the eloquence of the injured tissue.[43,44] In a post hoc analysis of HERMES, the involvement of the internal capsule was associated with unfavorable modified Rankin Scale-shifts (aOR, 0.44 [95% CI, 0.34–0.56]).[41] Rajashekar et al[45] described an increased precision of predicting 24 hour NIHSS by analyzing the structural integrity of white matter tracts on postinterventional imaging in a subgroup of patients included in the ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) and INTERRSeCT (Identifying New Approaches to Optimize Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV tPA Using Serial CT Angiography) Study. However, not all patients undergo follow-up MRI, which allows for an adequate delineation of functionally relevant areas involved. In our study, hemorrhagic transformation within the putamen was associated with an IC+ pattern, and the risk of observing an IC+ pattern was more than doubled in patients with evidence of hemorrhagic transformations

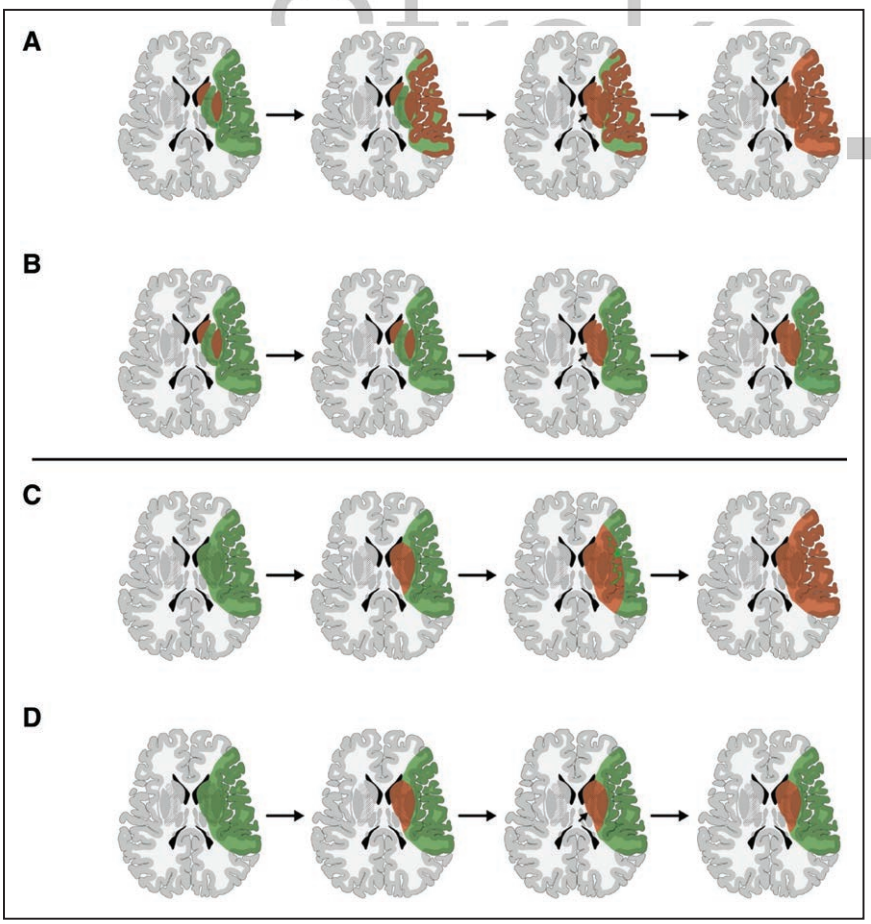

Figure 4. Hypothetical infarct growth model in a typical proximal M1 occlusion.
Infarct core and penumbra are displayed in red and green, respectively. Arrows between schematic drawings represent elapsing time from symptom-onset. **A** and **B**, Hypothetical refined infarct model with poor (**A**) and good (**B**) collaterals taking into account different collateralization of the lenticulostriate and peripheral middle cerebral artery territory as well as different susceptibility to hypoperfusion in gray and white matter, respectively; **C** and **D**, Infarct evolution model without tissue-selective discrimination with poor (**C**) and good (**D**) collaterals.

in the lenticulostriate artery territory. Several studies have shown that hemorrhagic transformations correlate with the severity of ischemia,[46] which may explain this association.

In a preceding study, in which we assessed the occurrence of white matter infarctions after MCA occlusion globally (ie, not focusing on the IC), sparing of the white matter (including the subcortical and deep white matter) by thrombectomy was also time-dependent, but the time dependency of white matter involvement was modulated by collateral grades.[17,18] In contrast, collateral grades appeared to have no impact on IC— involvement in the present study, as one would expect given the proven lack of an anatomic substrate for collateral supply to the LSA territories.

Thus, these observations also have implications for estimations and modeling of infarct growth, which may influence patient selection. Given the findings from this and other studies,[17,18] a refined hypothetical model of infarct evolution with a typical sequence is suggested (see Figure 4A and 4B versus classical pattern Figure 4C and 4D). Infarct evolution of the MCA lenticulostriate artery territory may be largely independent of collateralization and hence follow a time-rigid sequential ischemia of gray and white matter. However, the evolution of gray and white matter infarction in the peripheral MCA territory will depend on both, time and collateralization. Hence, infarct sequences may vary. Such a potentially clinically relevant, model is usually not well captured in current estimations of infarct cores and to the best of our knowledge no commercially available vendor has implemented different thresholds for grey and white matter yet.

Limitations

First, the final study population consisted of 92 patients only. This was partially related to the exclusion of patients with distal MCA or M2 occlusions but also because many patients did not receive a follow-up MRI. Confinement to postinterventional MRI may thus have introduced significant selection biases because patients with poor neurological status or otherwise more severe morbidity were less likely to undergo a follow-up MRI examination. Second, the study population is constituted by a European sample without intracranial stenosis as stroke cause, thus limiting generalizability to other populations with a higher prevalence of in-situ atherosclerotic disease of the proximal MCA. Third, some patients were lost to follow-up allowing for attrition bias. Fourth, the deduction of a refined infarct growth model is hypothetical and if validated, its benefit and feasibility for patient selection must be evaluated in prospective studies.

Conclusions

Rapid successful reperfusion of the lenticulostriate arteries often selectively protects the internal capsule from subsequent ischemia despite striatal infarction. Salvage of this eloquent white matter tract within the deep, non-collateralized MCA end artery territory seems strongly time-dependent, which has clinical and pathophysiological implications.

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Supplemental Materials

Online Table I
Online Figures I–IV

REFERENCES

1. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* 2015;372:11–20. doi: 10.1056/NEJMoa1411587
2. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, Guillemin F; THRACE investigators. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol.* 2016;15:1138–1147. doi: 10.1016/S1474-4422(16)30177-6
3. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905
4. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792
5. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061
6. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780
7. Loh Y, Towfighi A, Liebeskind DS, MacArthur DL, Vespa P, Gonzalez NR, Tateshima S, Starkman S, Saver JL, Shi ZS, et al. Basal ganglionic

infarction before mechanical thrombectomy predicts poor outcome. *Stroke*. 2009;40:3315–3320. doi: 10.1161/STROKEAHA.109.551705
8. Behme D, Kowoll A, Weber W, Mpotsaris A. M1 is not M1 in ischemic stroke: the disability-free survival after mechanical thrombectomy differs significantly between proximal and distal occlusions of the middle cerebral artery M1 segment. *J Neurointerv Surg*. 2015;7:559–563. doi: 10.1136/neurintsurg-2014-011212
9. Konishi J, Yamada K, Kizu O, Ito H, Sugimura K, Yoshikawa K, Nakagawa M, Nishimura T. MR tractography for the evaluation of functional recovery from lenticulostriate infarcts. *Neurology*. 2005;64:108–113. doi: 10.1212/01.WNL.0000148477.65273.0C
10. Decavel P, Vuillier F, Moulin T. Lenticulostriate infarction. *Front Neurol Neurosci*. 2012;30:115–119. doi: 10.1159/000333606
11. Kleine JF, Beller E, Zimmer C, Kaesmacher J. Lenticulostriate infarctions after successful mechanical thrombectomy in middle cerebral artery occlusion. *J Neurointerv Surg*. 2017;9:234–239. doi: 10.1136/neurintsurg-2015-012243
12. Friedrich B, Lobsien D, Maegerlein C, Wunderlich S, Zimmer C, Kaesmacher J, Kleine J. Distance to thrombus in acute middle cerebral artery stroke predicts basal ganglia infarction after mechanical thrombectomy. *Oncotarget*. 2016;7:85813–85818. doi: 10.18632/oncotarget.13280
13. Falcao AL, Reutens DC, Markus R, Koga M, Read SJ, Tochon-Danguy H, Sachinidis J, Howells DW, Donnan GA. The resistance to ischemia of white and gray matter after stroke. *Ann Neurol*. 2004;56:695–701. doi: 10.1002/ana.20265
14. Koga M, Reutens DC, Wright P, Phan T, Markus R, Pedreira B, Fitt G, Lim I, Donnan GA. The existence and evolution of diffusion-perfusion mismatched tissue in white and gray matter after acute stroke. *Stroke*. 2005;36:2132–2137. doi: 10.1161/01.STR.0000181066.23213.8f
15. Bristow MS, Simon JE, Brown RA, Eliasziw M, Hill MD, Coutts SB, Frayne R, Demchuk AM, Mitchell JR. MR perfusion and diffusion in acute ischemic stroke: human gray and white matter have different thresholds for infarction. *J Cereb Blood Flow Metab*. 2005;25:1280–1287. doi: 10.1038/sj.jcbfm.9600135
16. Berner LP, Cho TH, Haesebaert J, Bouvier J, Wiart M, Hjort N, Klærke Mikkelsen I, Derex L, Thomalla G, Pedraza S, et al. MRI assessment of ischemic lesion evolution within white and gray matter. *Cerebrovasc Dis*. 2016;41:291–297. doi: 10.1159/000444131
17. Rosso C, Colliot O, Valabrègue R, Crozier S, Dormont D, Lehéricy S, Samson Y. Tissue at risk in the deep middle cerebral artery territory is critical to stroke outcome. *Neuroradiology*. 2011;53:763–771. doi: 10.1007/s00234-011-0916-5
18. Kleine JF, Kaesmacher M, Wiestler B, Kaesmacher J. Tissue-selective salvage of the white matter by successful endovascular stroke therapy. *Stroke*. 2017;48:2776–2783. doi: 10.1161/STROKEAHA.117.017903
19. Kleine JF, Wunderlich S, Zimmer C, Kaesmacher J. Time to redefine success? TICI 3 versus TICI 2b recanalization in middle cerebral artery occlusion treated with thrombectomy. *J Neurointerv Surg*. 2017;9:117–121. doi: 10.1136/neurintsurg-2015-012218
20. Rosner SS, Rhoton AL Jr, Ono M, Barry M. Microsurgical anatomy of the anterior perforating arteries. *J Neurosurg*. 1984;61:468–485. doi: 10.3171/jns.1984.61.3.0468
21. Donzelli R, Marinkovic S, Brigante L, de Divitiis O, Nikodijevic I, Schonauer C, Maiuri F. Territories of the perforating (lenticulostriate) branches of the middle cerebral artery. *Surg Radiol Anat*. 1998;20:393–398. doi: 10.1007/BF01653128
22. Berkhemer OA, Jansen IG, Beumer D, Fransen PS, van den Berg LA, Yoo AJ, Lingsma HF, Sprengers ME, Jenniskens SF, Lycklama À Nijeholt GJ, et al; MR CLEAN Investigators. Collateral status on baseline computed tomographic angiography and intra-arterial treatment effect in patients with proximal anterior circulation stroke. *Stroke*. 2016;47:768–776. doi: 10.1161/STROKEAHA.115.011788
23. Marinkovic SV, Milisavljevic MM, Kovacevic MS, Stevic ZD. Perforating branches of the middle cerebral artery. Microanatomy and clinical significance of their intracerebral segments. *Stroke*. 1985;16:1022–1029. doi: 10.1161/01.str.16.6.1022
24. Takahashi S, Ishii K, Matsumoto K, Higano S, Kurihara N, Fukasawa H, Sakamoto K. Multiplanar MRI of cerebral infarcts along the distribution of the basal perforating arteries. In: Takahashi M, Korogi Y, Moseley I, eds. *Proceedings of the XV Symposium Neuroradiologicum*. Springer Berlin Heidelberg; 1995:98–99.
25. Takahashi S, Goto K, Fukasawa H, Kawata Y, Uemura K, Suzuki K. Computed tomography of cerebral infarction along the distribution of the basal perforating arteries. Part I: Striate arterial group. *Radiology*. 1985;155:107–118. doi: 10.1148/radiology.155.1.3975388
26. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, Gerig G. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage*. 2006;31:1116–1128. doi: 10.1016/j.neuroimage.2006.01.015
27. Kerr DM, Fulton RL, Lees KR; VISTA Collaborators. Seven-day NIHSS is a sensitive outcome measure for exploratory clinical trials in acute stroke: evidence from the Virtual International Stroke Trials Archive. *Stroke*. 2012;43:1401–1403. doi: 10.1161/STROKEAHA.111.644484
28. Kaesmacher J, Maegerlein C, Kaesmacher M, Zimmer C, Poppert H, Friedrich B, Boeckh-Behrens T, Kleine JF. Thrombus migration in the middle cerebral artery: incidence, imaging signs, and impact on success of endovascular thrombectomy. *J Am Heart Assoc*. 2017;6:e005149.
29. Masatoshi K, Reutens DC, Peter W, Thanh P, Romesh M, Bruno P, Greg F, Indra L, Donnan GA. The Existence and evolution of diffusion–perfusion mismatched tissue in white and gray matter after acute stroke. *Stroke*. 2005;36:2132–2137.
30. Chen C, Bivard A, Lin L, Levi CR, Spratt NJ, Parsons MW. Thresholds for infarction vary between gray matter and white matter in acute ischemic stroke: A CT perfusion study. *J Cereb Blood Flow Metab*. 2019;39:536–546. doi: 10.1177/0271678X17744453
31. Arakawa S, Wright PM, Koga M, Phan TG, Reutens DC, Lim I, Gunawan MR, Ma H, Perera N, Ly J, et al. Ischemic thresholds for gray and white matter: a diffusion and perfusion magnetic resonance study. *Stroke*. 2006;37:1211–1216. doi: 10.1161/01.STR.0000217258.63925.6b
32. Marinković SV, Kovačević MS, Marinković JM. Perforating branches of the middle cerebral artery. *J Neurosurg*. 1985;63:266–271.
33. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11–21. doi: 10.1056/NEJMoa1706442
34. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, et al; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718. doi: 10.1056/NEJMoa1713973
35. Hedderich DM, Boeckh-Behrens T, Friedrich B, Wiestler B, Wunderlich S, Zimmer C, Fischer U, Kleine JF, Kaesmacher J. Impact of time to endovascular reperfusion on outcome differs according to the involvement of the proximal MCA territory. *J Neurointerv Surg*. 2018;10:530–536. doi: 10.1136/neurintsurg-2017-013319
36. Santos EM, Marquering HA, den Blanken MD, Berkhemer OA, Boers AM, Yoo AJ, Beenen LF, Treurniet KM, Wismans C, van Noort K, et al; MR CLEAN Investigators. Thrombus permeability is associated with improved functional outcome and recanalization in patients with ischemic stroke. *Stroke*. 2016;47:732–741. doi: 10.1161/STROKEAHA.115.011187
37. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain*. 2007;130(pt 1):170–180. doi: 10.1093/brain/awl333
38. Zhu LL, Lindenberg R, Alexander MP, Schlaug G. Lesion load of the corticospinal tract predicts motor impairment in chronic stroke. *Stroke*. 2010;41:910–915. doi: 10.1161/STROKEAHA.109.577023
39. Sterr A, Shen S, Szameitat AJ, Herron KA. The role of corticospinal tract damage in chronic motor recovery and neurorehabilitation: a pilot study. *Neurorehabil Neural Repair*. 2010;24:413–419. doi: 10.1177/1545968309348310
40. Lam TK, Binns MA, Honjo K, Dawson DR, Ross B, Stuss DT, Black SE, Chen JJ, Fujioka T, Chen JL. Variability in stroke motor outcome is explained by structural and functional integrity of the motor system. *Sci Rep*. 2018;8:9480. doi: 10.1038/s41598-018-27541-8
41. Boers AMM, Jansen IGH, Beenen LFM, Devlin TG, San Roman L, Heo JH, Ribó M, Brown S, Almekhlafi MA, Liebeskind DS, et al. Association of follow-up infarct volume with functional outcome in acute ischemic stroke: a pooled analysis of seven randomized trials. *J Neurointerv Surg*. 2018;10:1137–1142. doi: 10.1136/neurintsurg-2017-013724
42. Boers AMM, Jansen IGH, Brown S, Lingsma HF, Beenen LFM, Devlin TG, Román LS, Heo JH, Ribó M, Almekhlafi MA, et al. Mediation of the relationship between endovascular therapy and functional outcome by follow-up infarct volume in patients with acute ischemic stroke. *JAMA Neurol*. 2019;76:194–202. doi: 10.1001/jamaneurol.2018.3661
43. Ernst M, Boers AMM, Forkert ND, Berkhemer OA, Roos YB, Dippel DWJ, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Vettorazzi E, et

al; MR CLEAN trial investigators (www.mrclean-trial.org). Impact of ischemic lesion location on the mRS score in patients with ischemic stroke: a voxel-based approach. *AJNR Am J Neuroradiol.* 2018;39:1989–1994. doi: 10.3174/ajnr.A5821

44. Habegger S, Wiest R, Weder BJ, Mordasini P, Gralla J, Häni L, Jung S, Reyes M, McKinley R. Relating acute lesion loads to chronic outcome in ischemic stroke–an exploratory comparison of mismatch patterns and predictive modeling. *Front Neurol.* 2018;9:737.
45. Rajashekar D, Mouchès P, Fiehler J, Menon BK, Goyal M, Demchuk AM, Hill MD, Dukelow SP, Forkert ND. Structural integrity of white matter tracts as a predictor of acute ischemic stroke outcome. *Int J Stroke.* 2020;15:965–972. doi: 10.1177/1747493020915251
46. Tong DC, Adami A, Moseley ME, Marks MP. Relationship between apparent diffusion coefficient and subsequent hemorrhagic transformation following acute ischemic stroke. *Stroke.* 2000;31:2378–2384. doi: 10.1161/01.str.31.10.2378